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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 38/28</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 98/42368</b> <b>(43) International Publication Date:</b> 1 October 1998 (01.10.98)
<b>(21) International Application Number:</b> PCT/DK98/00108 <b>(22) International Filing Date:</b> 20 March 1998 (20.03.98)  <b>(30) Priority Data:</b> 0319/97 20 March 1997 (20.03.97) <b>DK</b>  <b>(71) Applicant (for all designated States except US):</b> NOVO NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bagsværd (DK).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> JENSEN, Steen [DK/DK]; Sophus Falcks Allé 34, DK-2791 Dragør (DK). HANSEN, Philip [DK/DK]; Skovmindevej 23B, DK-2840 Holte (DK).  <b>(74) Common Representative:</b> NOVO NORDISK A/S; Novo Allé, DK-2880 Bagsværd (DK).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> THERAPEUTIC POWDER FORMULATION FOR PULMONARY ADMINISTRATION, CONTAINING CRYSTALLINE INSULIN  <b>(57) Abstract</b>  A therapeutic powder formulation suitable for pulmonary administration comprising particles composed of human insulin or any analogue or derivative thereof and an enhancer which enhances the absorption of insulin in the lower respiratory tract is disclosed. The powder formulation has a better stability profile than powders of essentially the same composition prepared by spray drying, freeze-drying, vacuum drying and open drying.		

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THERAPEUTIC POWDER FORMULATION FOR PULMONARY ADMINISTRATION, CONTAINING CRYSTALLINE INSULIN

## Field of the invention

The present invention relates to a therapeutic powder formulation suitable for pulmonary administration comprising particles composed of human insulin or any analogue or derivative thereof and an enhancer which enhances the absorption of insulin in the lower respiratory tract.

## Background of the invention

Diabetes is a general term for disorders in man having excessive urine excretion as in diabetes mellitus and diabetes insipidus. Diabetes mellitus is a metabolic disorder in which the ability to utilize glucose is more or less completely lost. About 2 % of all people suffer from diabetes.

Since the introduction of insulin in the 1920's, continuous strides have been made to improve the treatment of diabetes mellitus. To help avoid extreme glycaemia levels, diabetic patients often practice multiple injection therapy, whereby insulin is administered with each meal.

In the treatment of diabetes mellitus, many varieties of insulin preparations have been suggested and used, such as regular insulin, Semilente<sup>®</sup> insulin, isophane insulin, insulin zinc suspensions, protamine zinc insulin and Ultralente<sup>®</sup> insulin. Some of the commercial available insulin preparations are characterized by a fast onset of action. Ideally, exogenous insulin is administered at times and in doses that would yield a plasma profile which mimics the plasma profile of endogenous insulin in a normal individual. Insulin preparations containing analogs of human insulin have shown an absorption profile very close to the normal plasma profile, e.g. Lys<sup>B28</sup>-Pro<sup>B29</sup> human insulin and Asp<sup>B28</sup> human insulin. However, these new insulin preparations still have to be injected in connection with a meal. In order to circumvent injections, administration of insulin via the pulmonary route could be an alternative elucidating absorption profiles which mimic the endogenous insulin without the need to inject the insulin.

### Description of the background art

Administration of insulin via the pulmonary route can be accomplished by either an aqueous solution or a powder preparation. A description of the details can be found in

several references, one of the latest being by Niven, Crit. Rev. Ther. Drug Carrier Sys, 12(2&3):151-231 (1995). One aspect covered in said review is the stability issue of protein formulations, aqueous solutions being less stable than powder formulation. So far, all powder formulations have been described as mainly amorphous.

- 5 It has been found that when insulin is combined with an appropriate absorption enhancer and is introduced into the lower respiratory tract in the form of a powder of appropriate particle size, it readily enters the systemic circulation by absorption through the layer of epithelial cells in the lower respiratory tract as described in US patent No. 5,506,203. The manufacturing process described in said patent, comprising dissolution of insulin at acid  
10 pH followed by a pH adjustment to pH 7.4 and addition of sodium taurocholate before drying the solution by a suitable method, results in a powder composed of human insulin and absorption enhancer in a ratio between 9:1 to about 1:1. The powder is characterized as mainly amorphous determined under a polarized light microscope.

## Description of the invention

### 15 Definitions

The expressions "crystalline" and "amorphous" as used herein corresponds to different states of a powder particle, distinguishable by the following method: An aliquot of particles of the powder are mounted in mineral oil on a clean glass slide. Examination using a polarized light microscope elucidates birefringence for crystalline particles.

- 20 The expression "enhancer" refers to a substance enhancing the absorption of insulin, insulin analogue or insulin derivative through the layer of epithelial cells lining the alveoli of the lung into the adjacent pulmonary vasculature, i.e. the amount of insulin absorbed into the systemic system is higher than the amount absorbed in the absence of enhancer.

- 25 By "analogue of human insulin" (or similar expressions) as used herein is meant human insulin in which one or more amino acids have been deleted and/or replaced by other amino acids, including non-codeable amino acids, or human insulin comprising additional amino acids, i.e. more than 51 amino acids.

By "derivative of human insulin" (or similar expressions) as used herein is meant human insulin or an analogue thereof in which at least one organic substituent is bound to one or

more of the amino acids.

In the present context the expression "powder" refers to a collection of essentially dry particles, i.e. the moisture content being below about 10 % by weight, preferably below 6 % by weight, and most preferably below 4 % by weight.

- 5 The present invention relates to a therapeutic powder formulation suitable for pulmonary administration comprising particles composed of human insulin or any analogue or derivative thereof and an enhancer which enhances the absorption of insulin in the lower respiratory tract, wherein at least 50% by weight of said particles are crystalline.

10 The crystalline powder formulation of insulin and enhancer elucidates a better stability profile than powders of essentially the same composition prepared by spray drying, freeze-drying, vacuum drying and open drying. This is probably due to the substantially crystalline state of the powder formulations of the present invention compared to the amorphous state of powders prepared by the other methods described. By this means it is possible to store the powder formulations of the present invention at room temperature in  
15 contrary to human insulin preparations for injections and some amorphous insulin powders without stabilizing agent which have to be stored between 2°C to 8°C.

Furthermore, the substantially crystalline powder formulation of insulin and enhancer elucidates better flowing properties than corresponding amorphous powder formulations.

- 20 Preferably, at least 75% by weight, more preferably at least 90% by weight, of said particles are crystalline.

The enhancer is advantageously a surfactant, preferably selected from the group consisting of salts of fatty acids, bile salts or phospholipids, more preferably a bile salt.

Preferred fatty acids salts are salts of C<sub>10-14</sub> fatty acids, such as sodium caprate, sodium laurate and sodium myristate.

- 25 Lysophosphatidylcholine is a preferred phospholipid.

Preferred bile salts are salts of ursodeoxycholate, taurocholate, glycocholate and taurodihydrofusidate. Still more preferred are powder formulations according to the invention wherein the enhancer is a salt of taurocholate, preferably sodium taurocholate.

- 30 The preferred analogues of human insulin are fast-acting insulin analogues, in particular analogues wherein position B28 is Asp, Lys, Leu, Val or Ala and position B29 is Lys or Pro; or des(B28-B30), des(B27) or des(B30) human insulin. The most preferred analogues are

Asp<sup>B28</sup> human insulin or Lys<sup>B28</sup>Pro<sup>B29</sup> human insulin.

The preferred derivatives of human insulin are derivatives comprising one or more lipophilic substituents. The preferred lipophilic insulins are acylated insulins such as those described in WO 95/07931, e.g. human insulin derivatives wherein the  $\epsilon$ -amino group of Lys<sup>B29</sup> contains an acyl substituent which comprises at least 6 carbon atoms.

The insulin derivative is most preferably selected from the group consisting of B29-N $\epsilon$ -myristoyl-des(B30) human insulin, B29-N $\epsilon$ -palmitoyl-des(B30) human insulin, B29-N $\epsilon$ -myristoyl human insulin, B29-N $\epsilon$ -palmitoyl human insulin, B28-N $\epsilon$ -myristoyl Lys<sup>B28</sup>Pro<sup>B29</sup> human insulin, B28-N $\epsilon$ -palmitoyl Lys<sup>B28</sup>Pro<sup>B29</sup> human insulin, B30-N $\epsilon$ -myristoyl-Thr<sup>B29</sup>Lys<sup>B30</sup> human insulin, B30-N $\epsilon$ -palmitoyl-Thr<sup>B29</sup>Lys<sup>B30</sup> human insulin, B29-N $\epsilon$ -(N-palmitoyl- $\gamma$ -glutamyl)-des(B30) human insulin, B29-N $\epsilon$ -(N-lithocholyl- $\gamma$ -glutamyl)-des(B30) human insulin, B29-N $\epsilon$ -( $\omega$ -carboxyheptadecanoyl)-des(B30) human insulin and B29-N $\epsilon$ -( $\omega$ -carboxyheptadecanoyl) human insulin.

In a preferred embodiment the powder formulation of the present invention comprises an insulin derivative as well as human insulin or an analogue thereof.

However, human insulin is the most preferred insulin to be used in the formulation of the present invention.

In a particular embodiment of the present invention the powder formulation further comprises zinc, preferably in an amount corresponding to 2 Zn atoms/insulin hexamer to 12 Zn atoms/insulin hexamer, more preferably 4 Zn atoms/insulin hexamer to 12 Zn atoms/insulin hexamer or 2 Zn atoms/insulin hexamer to 10 Zn atoms/insulin hexamer, still more preferably 2 Zn atoms/insulin hexamer to 5 Zn atoms/insulin hexamer. By means of adding zinc to the preparations it is possible to adjust the timing, i.e. obtain the desired biological response within a defined time span, of the formulation as preparations with 0 - 10 Zn atoms/insulin hexamer elucidates different solubility properties determined in vitro with a 7 mM phosphate buffer solution.

In a preferred embodiment of the present invention, the major part of the crystals of the powder formulation have a maximum diameter of up to 10  $\mu$ m, preferably up to 7.5  $\mu$ m, more preferably up to 5  $\mu$ m. Powder formulations in which at least 80% or essentially all crystals have a maximum diameter within the above range are most preferred.

The molar ratio of insulin to enhancer in the powder formulation of the present invention is preferably 9:1 to 1:9, more preferably between 5:1 to 1:5, and still more preferably between 3:1 to 1:3.

5 The powder formulations of the present invention may optionally be combined with a carrier or excipient generally accepted as suitable for pulmonary administration. The purpose of adding a carrier or excipient may be as a bulking agent, stabilizing agent or an agent improving the flowing properties.

10 Suitable carrier agents include 1) carbohydrates, e.g. monosaccharides such as fructose, galactose, glucose, sorbose, and the like; 2) disaccharides, such as lactose, trehalose and the like; 3) polysaccharides, such as raffinose, maltodextrins, dextrans, and the like; 4) alditols, such as mannitol, xylitol, and the like; 5) inorganic salts, such as sodium chloride, and the like; 6) organic salts, such as sodium citrate, sodium ascorbate, and the like. A preferred group of carriers includes trehalose, raffinose, mannitol, sorbitol, xylitol, inositol, sucrose, sodium chloride and sodium citrate.

15 In a preferred embodiment the therapeutic powder formulation according to the invention comprises a stabilizing amount of a phenolic compound, preferably in an amount corresponding to at least 3 molecules of phenolic compound/insulin hexamer. The phenolic compound is preferably phenol, m-cresol, or a mixture of these compounds.

20 The powder formulation of the present invention may be produced according to the following general procedure:

Crystallization of insulin and the enhancer is accomplished by dissolving insulin in a dilute acidic solution, e.g. at a pH = 3.0 - 3.9, optionally adding a desired amount of zinc, e.g. corresponding to preferably 2 Zn atoms/insulin hexamer to 10 Zn atoms/insulin hexamer, more preferably 2 Zn atoms/insulin hexamer to 5 Zn atoms/insulin hexamer. Finally, the insulin/zinc solution is mixed under slight agitation with a solution of the enhancer. The proportion of insulin and enhancer on a weight basis when mixing the solutions is preferably between 9:1 to 1:9, more preferably between 5:1 to 1:5, and still more preferably between 3:1 to 1:3. The pH of the preparation is then adjusted to a value in the range of 4.5 to 7.4, preferably 4.5 to 7, more preferably 4.5 to 6.5, still more preferably 5.5 to 6.2, most preferably 5.5 to 6.1, and allowed to stand at rest for approximately 16 hours at a temperature between 20°C to 34°C, more preferable between 20°C to 25°C. The crystals formed are isolated by vacuum evaporation. The insulin powder can, if necessary, be micronized.

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This invention is further illustrated by the following examples which, however, are not to be construed as limiting.

#### EXAMPLE I

249.8 mg human insulin was dissolved in water by adding 2N HCl resulting in a pH = 3.7-3.8. 50  $\mu$ L 4 % Zinc chloride solution was added to the insulin solution while mixing. Water was added to 10 mL. 1g sodium taurocholate was dissolved in 10 mL water. Another insulin solution without the addition of zinc chloride was prepared by dissolving 251.6 mg human insulin in water by adding 2N HCl resulting in a pH = 3.6 - 3.7.

To three beakers were added 400 $\mu$ L, 450  $\mu$ L and 500  $\mu$ L, respectively, of the sodium taurocholate solution. 1.6 mL of the insulin solution containing zinc chloride was then added to each beaker while mixing. Water ad 10 mL was finally added while mixing.

To three other beakers were added 400 $\mu$ L, 450  $\mu$ L and 500  $\mu$ L, respectively, of the sodium taurocholate solution. 1.6 mL of the insulin solution without zinc chloride was then added to each beaker while mixing. Water ad 10 mL was finally added while mixing.

The pH was adjusted to 6.1 while mixing in all six beakers. After standing at rest for approximately 16 hours at 20°C - 25°C, crystals were formed in all preparations.

An aliquot of each preparation elucidates almost complete crystalline state of the particles as determined under a polarized light microscope. The size of the individual crystals was determined to 1 $\mu$ m - 5 $\mu$ m.

The supernatant was carefully removed from each of the preparations and the remaining wet crystalline fraction was dried by placing in a vacuumdryer for approximately 5 hours.

The dry insulin powders were analyzed by RP-HPLC for the content of human insulin and sodium taurocholate and the results showed a proportion of human insulin and sodium taurocholate of 4:1 to 2:1 depending on the content of sodium taurocholate. No difference was observed between the preparations with and without zinc chloride

#### EXAMPLE II

625.9 mg human insulin was dissolved in water by adding 2N HCl resulting in a pH = 3.6-3.7. 125  $\mu$ L 4 % Zinc chloride solution was added to the insulin solutions while mixing.



Water was added to 25 mL. 1g sodium taurocholate was dissolved in 10 mL water. To 16 mL of the insulin solution was then added 4 mL of the taurocholate solution while mixing. Water ad 100 mL was finally added while mixing. The preparation with the spontaneous amorphous precipitate was divided in 7 beakers with 10 mL in each. The pH was adjusted to 4.5, 5.0, 5.5, 6.0, 6.1, 6.5, 7.0 and 7.4 while mixing. After standing at rest for approximately 16 hours at 20°C - 25°C, crystals were formed in all preparations.

An aliquot of each preparation elucidates almost complete crystalline state of the particles as determined under a polarized light microscope. The size of the individual crystals was determined to 1µm - 5µm.

The supernatant was carefully removed from each of the preparations and the remaining wet crystalline fraction was dried by placing in a vacuumdryer for approximately 5 hours.

The dry insulin powders were analyzed by RP-HPLC for the content of human insulin and sodium taurocholate and the results showed a proportion of human insulin and sodium taurocholate of 6:1 to 3:1 depending on the actual pH value

### EXAMPLE III

625.9 mg human insulin was dissolved in water by adding 2N HCl resulting in a pH = 3.6-3.7. Water was added to 25 mL. 1g sodium taurocholate was dissolved in 10 mL water. The insulin solution was divided in 5 beakers with 4 mL in each. A 0.4 % Zinc chloride solution was added to the insulin solutions while mixing in an increasing amount: 81 µL, 123 µL, 164µL, 205µL, 285µL and 410µL. To each of the solutions were then added 1 mL of the taurocholate solution while mixing. Water ad 25 mL was finally added while mixing. The pH was adjusted to 6.1 while mixing. Spontaneously, an amorphous precipitate was formed in each of the preparations. After standing at rest for approximately 16 hours at 20°C - 25°C, crystals were formed in all preparations.

An aliquot of each preparation elucidates almost complete crystalline state of the particles as determined under a polarized light microscope. The size of the individual crystals was determined to 1µ - 5µ.

The supernatant was carefully removed from each of the preparations and the remaining wet crystalline fraction was dried by placing in a vacuumdryer for approximately 5 hours.

The dry insulin powders were analyzed by RP-HPLC for the content of human insulin and sodium taurocholate and the results showed a proportion of human insulin and sodium taurocholate of 6:1 to 4:1 depending on the content of zinc.

#### EXAMPLE IV

- 5 625,3 mg human insulin was dissolved in water by adding 2N HCl resulting in a pH= 3.6-3.7. 125 $\mu$ L 4 % Zinc chloride solution was added to the insulin solution while mixing. Water was added to 25 mL. 1 g sodium taurocholate was dissolved in 10 mL water. The insulin solution was divided in 4 beakers with 1.6 mL in each. To each of the beakers were added 400  $\mu$ L of taurocholate solution while mixing. A sodium chloride solution (100  
10 mg/mL) was added while mixing in an increasing amount: 0  $\mu$ L, 58 $\mu$ L, 116 $\mu$ L and 232 $\mu$ L. Water ad 10 mL was finally added while mixing. The pH was adjusted to 6.1 while mixing.

- 15 An aliquot of each preparation elucidates 50% to 80% crystalline state of the particles as determined under a polarized light microscope. The size of the individual crystals was determined to 1 $\mu$  - 5 $\mu$ .

The dry insulin powders were analyzed for the content of human insulin and sodium taurocholate and the results showed a proportion of human insulin and sodium taurocholate of 3:1 in all the preparations

#### 20 EXAMPLE V

- 2.5 g human insulin was dissolved in water by adding 2N HCl resulting in a pH = 3.6 - 3.7. 500  $\mu$ L 4 % Zinc chloride solution was added to the insulin solutions while mixing. Water was added to 100 mL. 2.5 g sodium taurocholate was dissolved in 25 mL water. The insulin solution was divided in 9 beakers with 8 mL in each. To 3 insulin solutions (group 1)  
25 were added 2 mL, to the next 3 insulin solutions (group 2) were added 2.25 mL and to the last 3 insulin solutions (group 3) were added 2.50 mL of the taurocholate solution while mixing. In each of the 3 groups, a sodium chloride solution 100 mg/mL was added in increasing amounts: 0  $\mu$ L, 290  $\mu$ L and 1160  $\mu$ L. Water ad 50 mL was finally added while  
30 mixing. The pH was adjusted to 6.1 while mixing. Spontaneously, an amorphous precipitate was formed in each of the preparations. After standing at rest for approximately 16 hours at 20°C - 25°C, crystals were formed in all preparations.

An aliquot of each preparation elucidates almost complete crystalline state of the particles with no sodium chloride added while the preparations with sodium chloride elucidate approximately 50 % to 80 % crystalline state as determined under a polarized light microscope. The size of the individual crystals was determined to 1 $\mu$  - 5 $\mu$ .

- 5 The supernatant was carefully removed from each of the preparations and the remaining wet crystalline fraction was dried by placing in a vacuum dryer for approximately 5 hours.

The dry insulin powders were analyzed for the content of human insulin and sodium taurocholate and the results showed a proportion of human insulin and sodium taurocholate of 6:1 to 3:1 in the preparations.

## Claims

1. A therapeutic powder formulation suitable for pulmonary administration comprising particles composed of human insulin or any analogue or derivative thereof and an enhancer which enhances the absorption of insulin in the lower respiratory tract, wherein at least 50% by weight of said particles are crystalline.
2. A therapeutic powder formulation according to claim 1 wherein at least 75% by weight, preferably at least 90% by weight, of said particles are crystalline.
3. A therapeutic powder formulation according to claim 1 or 2 wherein the enhancer is a surfactant.
4. A therapeutic powder formulation according to claim 3 wherein the surfactant is a salt of a fatty acid, a bile salt or a phospholipid, preferably a bile salt.
5. A therapeutic powder formulation according to claim 4 wherein the surfactant is a salt of taurocholate, preferably sodium taurocholate.
6. A therapeutic powder formulation according to anyone of the preceding claims which further comprises zinc in an amount corresponding to 2 Zn atoms/insulin hexamer to 12 Zn atoms/insulin hexamer, preferably 4 Zn atoms/insulin hexamer to 12 Zn atoms/insulin hexamer.
7. A therapeutic powder formulation according to claim 6 which comprises zinc in an amount corresponding to 2 Zn atoms/insulin hexamer to 10 Zn atoms/insulin hexamer, preferably 2 Zn atoms/insulin hexamer to 5 Zn atoms/insulin hexamer.
8. A therapeutic powder formulation according to anyone of the preceding claims wherein the major part of the crystals have a maximum diameter of up to 10  $\mu\text{m}$ , preferably up to 7.5  $\mu\text{m}$ .
9. A therapeutic powder formulation according to anyone of the preceding claims wherein the molar ratio of insulin to enhancer is 9:1 to 1:9, preferably between 5:1 to 1:5, and more preferably between 3:1 to 1:3.
10. A therapeutic powder formulation according to anyone of the preceding claims which further comprises a carrier, preferably selected from the group consisting of trehalose, raffinose, mannitol, sorbitol, xylitol, inositol, sucrose, sodium chloride and sodium citrate.

11. A therapeutic powder formulation according to anyone of the preceding claims which further comprises a stabilizing amount of a phenolic compound.
12. A therapeutic powder formulation according to claim 11 which comprises at least 3 molecules of a phenolic compound/insulin hexamer.
- 5 13. A therapeutic powder formulation according to claim 11 or 12 which comprises m-cresol or phenol, or a mixture thereof.
14. A method of treating diabetes, comprising administering to a subject in need thereof a therapeutically effective amount of the powder formulation according to anyone of the preceding claims.
- 10 15. A method of treating diabetes, comprising administering by pulmonary delivery to a subject in need of such treatment a therapeutically effective amount of a rapid-acting insulin analogue, preferably Lys<sup>B28</sup>-Pro<sup>B29</sup> human insulin or Asp<sup>B28</sup> human insulin.

# 1

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/DK 98/00108

### A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 38/28

According to International Patent Classification (IPC) or to both national classification and IPC

### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07K, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, PAJ, EPODOC, MEDLINE

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9619207 A1 (ASTRA AKTIEBOLAG), 27 June 1996 (27.06.96)	1-5,8-10
Y	--	6,7,11-13
Y	EP 0025868 A1 (HOECHST AKTIENGESSELLSCHAFT), 1 April 1981 (01.04.81), page 1	6,7
Y	EP 0709395 A2 (ELI LILLY AND COMPANY), 1 May 1996 (01.05.96), example 1	11-13
A	WO 9500128 A1 (ASTRA AKTIEBOLAG), 5 January 1995 (05.01.95)	1-13
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☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"&" document member of the same patent family

Date of the actual completion of the international search

22 June 1998

Name and mailing address of the ISA/  
Swedish Patent Office  
Box 5055, S-102 42 STOCKHOLM  
Facsimile No. +46 8 666 02 86

Date of mailing of the international search report

27.06.98

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 98/00108

**Box I** Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 14, 15  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Methods for treatment of the human body by surgery or therapy, see  
PCT Rule 39.1(iv)
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such  
an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II** Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**  
Information on patent family members

09/06/98

International application No.  
PCT/DK 98/00108

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9619207 A1	27/06/96	AU 4359296 A	10/07/96
		CA 2206803 A	27/06/96
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